



PATENT
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Ram PRATAP, et al

Serial No.: 09/316,313

Group No.: 1625

Filed: May 21, 1999

Examiner: E. Huang

For: METHOD FOR THE TREATMENT OF MALARIA BY THE USE OF PRIMAQUINE
DERIVATIVE N¹-(3-ETHYLIDINOTETRAHYDR-2-ONE)-N⁴-(6-METHOXY-8-
QUINOLINYL)-1,4-PENTANEDIAMINE AS GAMETOCYTOCIDAL AGENTS

Attorney Docket U-012254-3

Commissioner Patents and Trademarks
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SECOND AMENDMENT AFTER FINAL REJECTION

Sir:

Further to Applicants' Amendment dated 23 July 2001, and in supplemental response to the Official Action of 22 February 2001, Applicants annex hereto copies of literature references which support Applicants' position that the primary reference cited by the Examiner, Andersag, would **not** convey to one of skill in the art that all compounds within the genus described by Andersag would be therapeutically effective in treating malaria. The annexures are described

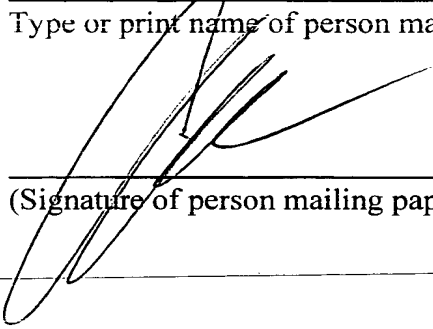
CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner of Patents and Trademarks, Washington, DC 20231

CLIFFORD J. MASS

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below.

1. Annexure I:

Carson, P.E. '8 *Aminoquinoline*' 1984, Antimalarial Drugs II, Eds. Peters and Richards, teaches on page 100 that 8 - aminoquinolines are active different stages of life cycle of the malaria parasite. It also teaches that studies of radical cure with prevention of relapses, causal prophylaxis, and sporontocidal and gametocytocidal effects must be considered separately from each other even for the same anti-malarial drug. On page 83 it is taught that primaquine has significant toxic effects.

Andersag does not clarify which of the above activities were carried out to qualify the 8-aminoquinolines as antiparasitic since the available antimalarial screening tests before 1945 relied on blood schizontocidal efficacy in avian malaria models. Support for this is found in Annexure II below.

2. Annexure II

Wiselogle, '*A survey of antimalarial drugs 1941 - 1945*', Wiselogle, J.W. Edwards, 1946 surveys the activity of about 13000 potential compounds. The tests used were blood schizontocidal efficacy in avian malaria models.

3. Annexure III

Sweeney, et al '*Chemotherapy & Immunology in control of malaria, filarial and leishmaniasis*', Gen Ed. Nityanand and A. B. Sen, Tata McGraw Hill Publishing Company, 1983.

This document summarizes the radical curative activity of 8- and 4-aminoquinoline antimalarial drugs (see Table 5.2). Briefly stated, it is clear from this teaching that various 8-aminoquinolines may not possess either of blood schizontocidal activity, causal prophylactic activity, radical curative activity or gametocytocidal activity. Thus, it is mandatory to screen new compounds against various test models to determine which antimalarial activity, if any, is present or absent in the new compounds. It is not possible to simply hypothesize or predicate certain forms of antimalarial activity to new compounds.

4. Annexure IV

Sweeney, T.R. '*8-aminoquinolines*', 1984, Antimalarial Drugs, Eds. Peters and Richards, Chapter 10.

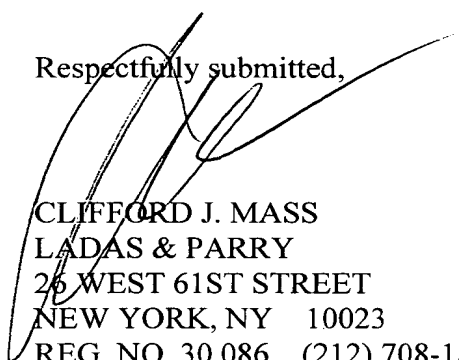
This document clearly teaches on page 339 that several 8-aminoquinolines show little or no blood schizontocidal activity.

Thus, while most 8-aminoquinolines may be antimalarials, not all show gametocytocidal activity. There are numerous examples of discovery of new gametocytocides which do not belong to the class of 8 aminoquinolines, such as dihydroacridine - diones, etc. It is not possible

to predict the gametocytocidal activity of a new compound without experimentation. Each compound has to be evaluated separately (or so it is believed in this field), for any of the several forms of antimalarial activity. Andersag does not refer to any particular type of antimalarial activity.

A favorable reconsideration of the application is again respectfully requested in view of the above.

Respectfully submitted,



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